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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Application/Patent No: 10/273,081 USPTO CONFIRMATION NO: 6230

Filed: 10/17/2002

Inventor/Title: McCallister, et al./ Effervescent Compositions Comprising Phosphonates and Methods Related Thereto

Examiner/Art Unit: Shaoha A. Jiang/1617

Declaration under 37 CFR §1.132

COMMISSIONER FOR PATENTS
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SIR:

I, Marshall A. Hayward, Ph.D., hereby make the following declaration:

1 I received a B.Sc. degree from Michigan State University in the year 1977 and a Ph.D. degree from the University of Illinois at Urbana-Champaign in1983.

2. From 1983 to 1988 I was employed by the company that is now Wyeth as a Principal Scientist in Osteoporosis Research. From I988 to 1989 I was a Senior Scientist with Johnson and Johnson Health Care Company with responsibilities in wound care research. From 1989 through 1 997 I was with the company that is now Glaxo Smith Kline, with responsibilities in technology development and drug delivery, working under several titles and eventually as Director and Vice President, Analgesics Research and Development, From 1997 through 1999, I was with Rhodia Inc. as Director, Business Development. In 2000, I joined

Hurley Consulting Associates Ltd. as Vice President, Business Development. I am currently the Chief Scientific Officer of EffRx, Inc., with primary responsibilities in effervescent product development.

3. I have read the subject patent application, the rejections in the Office Action dated February 6, 2008, and the prior art cited against the invention (Katdare 5,853,759). I am fully familiar with the field of technology embraced by this patent application and the cited prior art.

4. In the last paragraph on page 4 of the Office Action, the Examiner states that:

> ...the ratio of the buffering agents to the total weight of effervescent composition is about the same as that of Katdare composition. In other words, if the total weight of Katdare's composition is about 3.5 to 6 grams (which is within the range of Katdare's composition), the buffering capacity would be increased to what is similar to that of the instant invention. See the ANC test of the compositions in declaration by Dr. Rohrich. The examiner also notes that the composition of claim 4 in Katdare is relatively close to 3.5 grams - if all the ingredients are in the maxim amount, the weight of the tablet is around 3.2-3.3 grams. Therefore, possessing the teachings of Katdare, one of ordinary skill in the art would be motivated to adjust the amounts of the ingredients to the herein claimed amounts.

5. Since the dose of alendronate in Katdare is 10 mg, which that of the present invention is 50 – 120 mg, the Examiner appears to be assuming that a person of ordinary skill in the art would have increased the amount of buffering components and other excipients automatically after it was decided to increase the dose of alendronate. However, that assumption is not correct.

6. Effervescent pharmaceutical formulations are typically designed to be dissolved in 100 to 200 ml of water regardless of the dosing strength, with the volume largely dependent upon the nature of the active ingredients (drug, vitamin, mineral, or other nutritional product) and the commercial objective. The effervescent form itself simply provides a means of dispersing the drug into water

solution for easy consumption, particularly for drugs where there is a large dosage. The solution is often flavored to mask the taste of any disagreeable components such as acetaminophen, especially when these are present in large amounts. For example, in the case of acetaminophen, where the dose is up to 1000 mg, a large volume of water (about 250 ml) is used to help dilute the dosing solution, increasing palatability. However, the tablet itself should be as small in volume as is practical, to reduce the cost of tablet ingredients, as well as to ensure good tableting and production properties. To address these issues, a 1000 mg dose of acetaminophen is provided commercially as 2 x 500 mg tablets for reconstitution, primarily to address taste issue, while allowing the tablets to be produced at a typically size.

7. As noted above, another practical consideration is the ability to manufacture effervescent tablets on a tablet press. Typical effervescent tablets have a maximum of diameter of 25 mm, and to ensure good tablet integrity and production, a maximum of 4 to 4.5 mm thickness is used.

8. The Katdare examples and the formula test below as representative thereof, are typical effervescent tablet formulas, whereas the EX101 formula is very large (thick) and thus atypical. Pharmaceutical tablets of 25 mm diameter which are thick are difficult (if not impossible) to produce and can suffer from the problems of delamination, picking, sticking, and breakage upon ejection from the tablet press. Generally an effervescent tablet is optimized with respect to the effervescent couple, size, and desired volume of liquid to be ingested. Once a product is developed, if a new or different dosage strength is desired (for example if the dosage is increased), the effervescent tablet base composition and volume for reconstitution is held constant if possible, and just the amount of the active ingredient is adjusted upward. Only in extraordinary circumstances, e.g. a very foul tasting drug, would the volume of ingestion and the flavor components be altered. Even in that case, the general effervescent components are not altered.

9. If the ingredients do not have a bad taste, the volume of the dosing solution is routinely kept to 50-100 ml or so. This volume of reconstitution is independent of the drug dose, so that in the case of ingredients where flavor is not an issue, the only variable is the amount of active ingredient in the tablet. That is the case with products such as vitamin C, where doses of 60 mg to 1000 mg are also delivered in a single tablet at a maximum volume of 200 ml (3 to 6 ounces or so).

10. Bisphosphonates in general, and alendronate in particular, has no taste and is readily soluble in water. Therefore, if the alendronate dose were raised from the very small 5 to 10 mg doses of Katdare, up to 70 mg or even more, there would be no logical basis to increase the amount of the effervescent couple or the excipients. To the contrary, from the standpoint of cost the smallest tablet that generates an effective solution for consumption would be selected. So a dosing volume of 100 to 200 ml would probably not be increased at all and certainly not by a factor of 7 when increasing the dose of alendronate from 10 mg to 70 mg, because that would result in a dosing volume of 700 to 1400 ml, which is a prohibitive volume for dosing. The Katdare examples are typical of effervescent formulations that are palatable for alendronate, independent of the dose and deliverable in a reasonable (100-200 ml volume).

11. In contrast, the present formulation was developed in order to control the pH of the stomach over time and the dosage of alendronate does not affect the amount of buffering capacity needed to achieve the desired results.

12. Under my direction, stomach pH and gastric emptying effects were evaluated in subjects treated with either an effervescent alendronate formulation that is representative of Katdare, or with a highly buffered alendronate solution (EX101), that is representative of the present invention. Oral administration of alendronate is associated with gastric intolerability. Toxicology data and clinical experience suggest that when alendronate is directly exposed to mucosal tissues (as when a tablet may stick in the in the esophagus), serious damage can result. Furthermore, reflux of alendronate in acidic gastric fluid can also be damaging. Alendronate

exists in the non-injurious salt form above pH 3, but under pH 3 (acidic conditions) it is present as the free acid form recognized to cause tissue damage.

13. Fosamax NDA 21-575 discusses the importance of pH effects on alendronate tolerability. The toxicology conclusions section of the biopharmaceutics review states:

> ...which suggest that multiple factors contribute to the development of clinical esophagitis including prolonged contact of the tablet with the mucosa, reflux of acidic gastric contents containing alendronate, and preexisting esophageal damage from a low pH environment (gastric reflux damage). Under acidic conditions (pH <3) alendronate exists in the free acid form (>67%) which is more irritating than the sodium salt form ..... The sponsor suggests that most of the clinical cases of esophagitis are associated with deviations from proper dosing. Irritation can be minimized by proper dosing and avoidance of conditions known to exacerbate gastric acid reflux.

14. A clear approach to improving alendronate tolerability is to minimize mucosal exposure to alendronate in an acidic environment.

15. EX 101 formula: alendronic acid (70 mg) as 91.37 mg alendronate sodium trihydrate, 1900 mg monosodium citrate anhydrous, 839.63 mg citric acid anhydrous, 751 mg of sodium bicarbonate, 430 mg of sodium carbonate anhydrous, 30 mg of strawberry flavor, 4 mg of acesulfame potassium, 4 mg of sucralose, and is granulated with 400 mg purified water (but the water is lost in processing and is not present in the final tablet).

16. The formulation representative of Katdare: Alendronic acid (70 mg) as 91.37 mg alendronate sodium trihydrate, 600 mg citric acid anhydrous, 1500 mg sodium bicarbonate, and 40 mg sodium carbonate anhydrous. While the alendronate dosage of 70 mg was higher than that used in the examples of Katdare (10 mg) that difference is not important to the results of these experiments because alendronate is not itself a significant buffering agent.

17. Fosamax tablets: alendronic acid (70 mg) as 91.37 mg alendronate sodium trihydrate in a conventional tablet matrix that contains microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. There are no effervescent or buffering components in this formulation.

18. Gastric emptying was judged by the time it takes for 50% and for 90% of the stomach contents to pass into the small intestine ("Gastric Emptying Time 50% Empty" or "Gastric Emptying Time 90% Empty" are abbreviated as "GET50" and "GET90" respectively). The data in Table 1 show no significant differences in emptying time between EX101 and Katdare. Furthermore the differences are not considered to be physiologically relevant. As most individuals taking alendronate may eat 30 minutes after ingesting the drug (that is, following the post-dose fast label instructions), any time beyond 30 minutes is probably not relevant to the tolerability of the dosing forms.

Table 1

Parameter	Fosamax	EX101	Katdare
	Time, minutes +/-SD	Time, minutes +/-SD	Time, minutes +/-SD
GET50	28.0 +/- 25.6	34.4 +/- 23.3	23.2 +/- 20.0
GET90	63.2 +/- 35.4	71.6 +/- 48.3	56.9 +/- 33.9

19. Gastric imaging and pH telemetry data correlate stomach pH with stomach content of alendronate solution. After swallowing EX101, we found that the stomach pH reaches pH 5 and is maintained above pH 3 until the stomach contents containing the alendronate pass into the intestine.

20. On average, Fosamax subjects returned to acidic stomach conditions (passing below pH 3) in 3.5 minutes (mean) or 1.8 minutes (median) after dosing.

21. On average, EX101 subjects crossed below the pH 3 threshold after 56.0 minutes (mean) or 25.2 minutes (median). Thus it was confirmed that EX101 is a gastroprotective formula. Furthermore, a rather large variability in the gastric emptying time suggests that the long period of elevated pH observed in EX101

subjects should provide greater gastric protection, especially for slow emptying subjects.

22. For the Katdare formula, the time to pH 3.0 threshold crossing was 23.7 minutes (mean) and 19.8 minutes (median), which is significantly less than EX101.

23. My conclusion is that EX101 provides and maintains alendronate in a non-acidic form for more than 30 minutes; indeed, for the entire time it is in the stomach, thus minimizing the risk of esophageal damage. That is because even if the solution were refluxed, the salt form of alendronate would be present, and that poses little risk of damage to the esophagus. So there is no practical risk of acidified alendronate exposure in the EX101 subjects.

24. A small but clearly identifiable risk of acidic alendronate exposure is associated with the Katdare formula since the time to pH 3.0 threshold crossing was only 23.7 minutes (mean) and 19.8 minutes (median) due to having significantly less buffering capacity, and, therefore, less gastroprotection during the critical first 30 minutes.

25. I declare that all statements made herein of my own knowledge are rue and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 7 July 2008 By: _____

Marshall A. Hayward, Ph.D.